

A Study of Four-Membered Cyclic-Ureas

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY,
IN THE UNIVERSITY OF MICHIGAN

By

Norbert Adolph Lange

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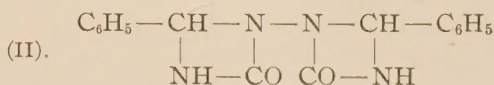
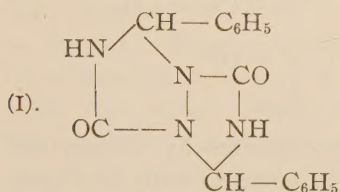
The author desires to express his gratitude to Professor William J. Hale for the valuable instruction and assistance received from him. This investigation was undertaken at his suggestion and has been carried out under his supervision.

CONTENTS.

I. History:	
Schiff's Work on the Condensation of Acetaldehyde and Urea.....	5
Preparation of Ethylidene Urea by Reynolds.....	6
The Condensation of Formaldehyde and Urea.....	6
Hemmelmayer's Preparation of Methylene-Urea by the Action of Chloromethyl Alcohol upon Urea.....	6
The Condensation of Formaldehyde and Urea in Acid, Alkaline and Neutral Solution.....	7
Condensation of Aldehydes and Thioureas.....	7
Condensation of Dithiobiurets with Aldehydes and Ketones.....	9
Interaction of Urea and Cyanoacetic Ester.....	10
Addition of Phenyl Isocyanate to Methylenaniline.....	10
Addition of Phenyl Isocyanate to <i>p</i> -Dimethyl-aminobenzaldehyde.....	11
II. Theoretical Considerations:	
Addition of Isocyanic Acid to Benzylidenaniline.....	13
Condensation of Benzaldehyde and Phenyl-Urea.....	14
Addition of Isocyanic Acid to Alkyl Schiff Bases.....	16
Influence of <i>N</i> -Amino Groups on the Addition of Isocyanic Acid to the Carbimino Nucleus.....	17
Hydrolysis of 1-Benzylidene-2-benzylsemicarbazone.....	18
Preparation of 2-Benzylsemicarbazide and Its Transformation into the 1-Benzylsemicarbazide.....	19
Condensation of Benzaldehyde with Hydrazodicarbonamide.....	23
III. Experimental Part:	
Preparation of Potassium Cyanate.....	24
Condensation of Isocyanic Acid and Benzylidenaniline.....	25
Condensation of Isocyanic Acid and Alkyl Schiff Bases.....	26
Condensation of <i>p</i> -Tolylazine and Isocyanic Acid.....	28
Hydrolysis of 1-Benzylidene-2-benzylsemicarbazone.....	28
Preparation of Pure 2-Benzylsemicarbazide.....	29
Preparation of 1-Benzylsemicarbazide.....	30
Action of Isocyanic Acid upon <i>N</i> -Amino Derivatives of the Carbimino Nucleus.....	30
Condensation of Benzaldehyde and Phenyl-Urea.....	30
Condensation of Hydrazodicarbonamide and Benzaldehyde.....	33
Summary.....	34
Bibliography.....	35

I. Historical Part.

In a paper published by Bailey and Moore,¹ it was shown that benzalazine, when dissolved in glacial acetic acid, readily takes up two molecules of cyanic acid. These authors considered the various possible structural formulas for the addition compound and finally decided upon a new type of binuclear triazole (I), as the best adapted to explain all of the conditions. It appeared to us that these authors had not considered in sufficient detail the possibility that the new compound might be of a type as represented in (II)—a bisbenzylidene-urea.



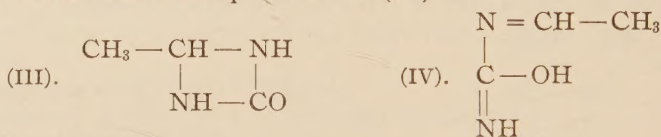
One of the reasons for their rejecting the structure II was the fact that no conclusive proofs had as yet been advanced to show that the so-called methylene-urea and its derivatives are in fact *cyclic-ureas*. It is necessary, therefore, that any discussion of the possibility of a cyclic-urea formula for the product obtained by Bailey and Moore must be preceded by a sketch of the facts already known which might support the possible cyclic-urea structure. A review of the literature shows that there existed considerable difference of opinion as to the mode of condensation of aldehydes and urea and of their structural characteristics.

The four-membered cyclic-urea structure was first proposed by H. Schiff² in 1869. Through a comprehensive study of a large number of condensations between urea and various aldehydes, it was observed that the product (III) resulting from the action of acetaldehyde upon urea, possessed properties slightly different from those products obtained when urea was brought into action with various aromatic aldehydes. When, for example, this ethylidene-urea of Schiff was boiled with aniline alone there followed a decomposition of the molecule into urea and acetaldehyde (the latter through further condensation with excess of aniline separated finally as a form of ethylidene-diphenylamine). On the other hand, the second type of Schiff's condensation products, known as ureides, decomposed under this same action of aniline in a similar manner, but with much greater difficulty. The ethylidene-urea possessed no basic properties whatsoever. It did not form salts with platinum or gold

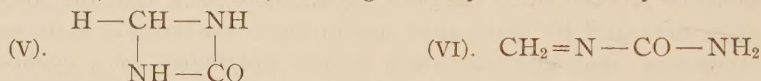
¹ *J. Am. Chem. Soc.*, **39**, 279 (1917).

² *Ann.*, **151**, 206 (1869).

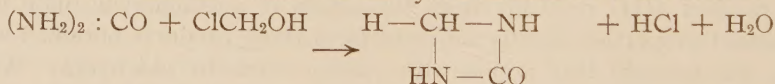
chlorides. Cold concentrated mineral acids or warm water sufficed for its hydrolysis into the original constituents. The compound melted with decomposition at about 160° and dissolved but slightly in the ordinary solvents. These observations of Schiff were mainly corroborated by J. E. Reynolds,³ who obtained ethylidene-urea by heating a saturated solution of urea in acetaldehyde in an autoclave at 100° . He, too, found that only one molecule of acetaldehyde condensed with a molecule of urea. From this Reynolds concluded that one hydrogen atom in urea was not replaceable by an aldehydic oxygen atom, but was of a different nature and therefore looked upon the compound as a derivative of pseudo-urea with the structure as represented in (IV).



The action of formaldehyde upon urea was reported by Tollens and Hölzer⁴ as yielding a white, insoluble substance identical with that compound prepared later by Lüdy⁵ in the condensation of urea with methylene chloracetin ($\text{ClCH}_2\text{C}_2\text{H}_3\text{O}_2$) and regarded by him as methylene-urea (V).



Hemmelmayer⁶ prepared methylene-urea by means of an entirely different reaction. Upon warming one molecular proportion of urea with one and one-half molecular proportions of chlormethyl alcohol, the urea gradually dissolved and, after cooling, the mixture solidified. He obtained a white substance extremely insoluble in all of the ordinary solvents. By analysis this product accorded with the formula $\text{C}_2\text{H}_4\text{ON}_2$ and was considered as methylene-urea. Hemmelmayer gave the following equation for the reaction and also indicated the cyclic structure for the ureide:



The action of mineral acids sufficed for its hydrolysis into the original constituents, whereas organic acids failed in this direction. The compound melted with decomposition at 240° . Its marked insolubility recalls this same property in the ethylidene-urea of Schiff. The condensation of formaldehyde with urea was reported by Carl Goldschmidt,^{7,8} as lead-

³ *Chem. News*, **24**, 87 (1871).

⁴ *Ber.*, **17**, 659 (1884).

⁵ *Monatsh.*, **10**, 295 (1889).

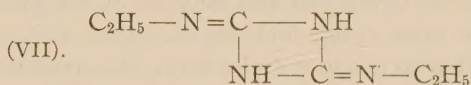
⁶ *Ibid.*, **12**, 94 (1891).

⁷ *Ber.*, **29**, 2438 (1896).

⁸ *Chemiker-Zeitung*, **21**, 460 (1897).

ing to several products—a compound, $C_5H_{10}O_3N_4$, insoluble in water if the condensation took place in acid medium; a dimethylol-urea, $CO-(NHCH_2OH)_2$, soluble in water, if in alkaline medium; and a variable mixture of these two if in neutral medium. Tollens⁹ and his co-workers obtained only an insoluble product which accorded by analysis with the formula as proposed by Lüdy (V) or with that of (VI). The inadequate description in Goldschmidt's reports led Einhorn and Hamburger¹⁰ to repeat these experiments. They ascertained the exact conditions necessary for the isolation of dimethylol-urea as well as mono-methylol-urea and found that the production of N-methylol compounds under such conditions is in exact agreement with results obtained by Einhorn¹¹ on acid amides and formaldehyde.

Several isolated cases may be cited where reference is made to four-membered cyclic-ureas. Among the condensation products of aldehydes and urea which Schiff described was an acrolein-di-ureide. Leeds,¹² without having any previous knowledge of Schiff's acrolein-di-ureide, prepared a condensation product in the same manner but found entirely different analytical results; the values indicated a mono-ureide. Biginelli¹³ assumed the cyclic-urea structure for one of the products obtained in the condensation of *m*-nitrobenzaldehyde and urea; Schiff (*loc. cit.*) reported the same product as a tri-ureide. H. Guillemard^{14,15} explained the condensation of ethyl carbylamine dibromide (ethyl iminocarbonyl bromide) with ammonia as proceeding to a compound of structure (VII).



The action of aniline and other amines upon this dibromide yielded, however, simple substituted guanidines as $C_2H_5.N:C:(NHR)_2$. Until further evidence is forthcoming there is no special reason to consider this action of ammonia as other than a substitution of the two bromine atoms by an imino group. The compound formed, $C_2H_5.N:C:NH$, would correspond in analysis to the values reported by Guillemard and would possess the marked basic properties which the compound displays.

The most important and comprehensive work on this type of cyclic compound is reported in a recent article by Dixon and Taylor¹⁶ on the interaction of aldehydes and thioureas. They found that a cold, aqueous

⁹ *Ber.*, **29**, 2751 (1896).

¹⁰ *Ibid.*, **41**, 24 (1908).

¹¹ *Ann.*, **343**, 207 (1905).

¹² *Ber.*, **15**, 1159 (1882).

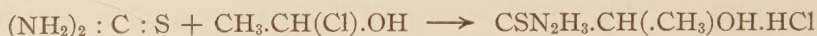
¹³ *Gazz. chim. ital.*, **23**, (I), 369 (1893).

¹⁴ *Bull. soc. chim.*, [3] **31**, 605 (1904).

¹⁵ *Ibid.*, [3] **33**, 652 (1905).

¹⁶ *J. Chem. Soc.*, **109**, 1244 (1916); *Ibid.*, **113**, 238 (1918).

solution of thiourea mixed with aldehyde remained clear if the mixture was kept neutral but on acidification a white solid was deposited which had the composition of a mono-ureide. This ureide originated through the spontaneous decomposition, in the presence of water, of an unstable base, the hydrochloride of which is producible from thiourea and α -chloroethyl alcohol, as shown below:



This addition compound yielded, on treatment with cold water, an acid solution; on neutralization of this solution, a base separated as a white, amorphous solid. This base gradually lost a molecule of water and changed into the insoluble condensation product. The composition of the intermediate unstable base was confirmed by that of the somewhat more stable ethoxyethyl iminothiocarbamate, the hydrochloride of which was produced on treating an alcoholic solution of acetaldehyde and thiourea in suspension with hydrogen chloride. Alkyl and aryl substituted thioureas, when treated with aldehyde and hydrogen chloride, were found to yield the corresponding hydrochlorides; these hydrochlorides were syrups which gradually harden on standing in a vacuum. With mono-substituted thioureas, the bases and condensation products were obtained, but with symmetrical diphenyl thiourea no condensation product was obtained because of the unstability of this product. This had previously been observed by Senier and Shephard.¹⁷ Because of the nature of the products obtained on hydrolysis and because of the preparation of what was evidently the same compounds by Reynolds (*loc. cit.*), who used a method not expected to produce an iso-form, the structure (VIII) is given preference over the isothiocarbamide structure (IX).

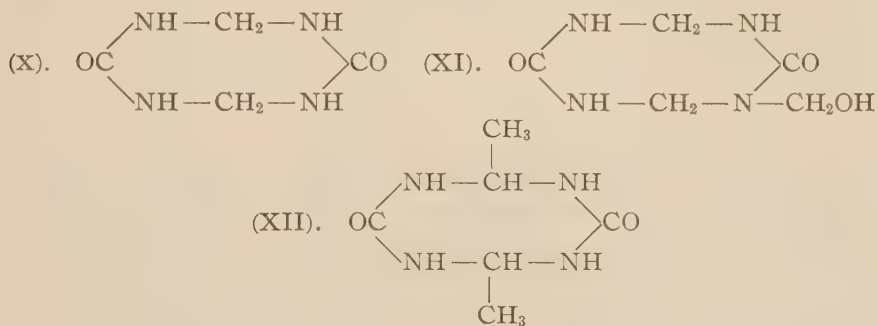


This work admirably explains the production of the comparatively stable methylol-urea, $\text{NH}_2.\text{CO}.\text{NH}.\text{CH}_2\text{OH}$, as the first product of the reaction. This compound may be expected to change into a chloro derivative, $\text{NH}_2.\text{CO}.\text{NH}.\text{CH}_2\text{Cl}$, under the influence of hydrogen chloride and finally yield a residue, $-\text{NH}.\text{CO}.\text{NH}.\text{CH}_2-$, which through simple polymerization could give the ring structure (X). This is indeed a polymer of the so-called "methylene-urea" (V), and from all of the characteristics of the compound accords best with its true structure (X). The work of Chattaway¹⁸ on dichloro-urea and its condensation to *p*-urazine is analogous. The presence of excess formaldehyde in the acid medium of the urea condensation would naturally be expected to produce a methylol

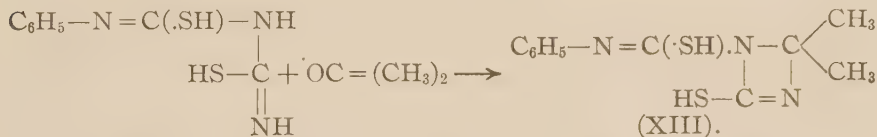
¹⁷ *J. Chem. Soc.*, 95, 495 (1909).

¹⁸ *Ibid.*, 95, 236 (1909).

derivative (XI) of "methylene-urea" and this portrays the probable constitution of Goldschmidt's (*loc. cit.*) compound, $C_5H_{10}O_3N_4$. Dimethylol-urea was best prepared by evaporation of a neutral solution of urea in sufficient formaldehyde and crystallization of residue from alcohol. Upon acidification of its aqueous solution, this compound as anticipated passed over into the Goldschmidt compound $C_5H_{10}O_3N_4$, with loss of water and formaldehyde. It would appear, therefore, that the amorphous insoluble products heretofore described as "methylene-urea" and also "ethylidene-urea" can no longer be explained upon the simple structures (V) and (III) but more favorably upon the structure (X) and (XII), respectively.



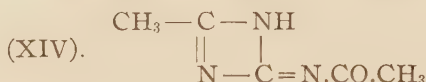
An unsaturated form of a four-membered heterocyclic ring containing two nitrogen atoms was first announced by Fromm.¹⁹ Through an exhaustive study of the condensations of various dithiobiurets with aldehydes and ketones, under the influence of dry hydrogen chloride, Fromm was able to establish the structure of the condensation products as derivatives of four-membered heterocyclic rings. Thus, from phenyl dithiobiuret and acetone, was obtained α -phenyl-dithio-di-C-methyl keturet (XIII).



The product was named an "alduret" if obtained by the action of an aldehyde and "keturet" if from a ketone (as illustrated above). Generally, these aldurets and keturets are high melting, crystalline substances; they are decomposed by concentrated acids liberating the aldehyde or ketone used in their formation, but comparatively stable in the presence of alkalis; they are insoluble in water, but more or less soluble in alcohol. There

¹⁹ *Ann.*, **275**, 20 (1893); *Ibid.*, **348**, 166 (1906); *Ibid.*, **394**, 282 (1912); *Ber.*, **28**, 1102 (1895).

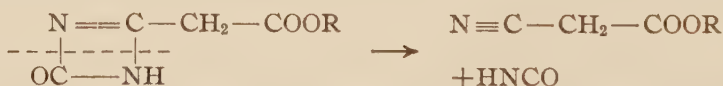
can be little or no doubt concerning the structure of this class of compounds as so well demonstrated by Fromm. A formula of similar structure (XIV) was proposed by Korndörfer²⁰ for the anhydride of diacetyl guanidine. Further investigation is here required to establish the claims set forth.



The most striking synthesis of an unsaturated four-membered cyclic urea was announced by Frerichs and Hartwig.^{21,22} These investigators heated urea with cyanoacetic ester and interpreted the reaction as proceeding between this latter and cyanic acid (isocyanic acid) liberated in the decomposition of urea.



The final product was considered as a derivative of a cyclomethine-urea in analogy to the Schiff formula for "methylene-urea." It is soluble in alcohol or ether but insoluble in water. It is acid in character and gives a red coloration with ferric chloride. Complete decomposition by strongly heating with aniline yielded ammonia and symmetrical diphenyl-urea. This fact led to the assumption that isocyanic acid as such was still present in the molecule, producing with the aniline first a monophenyl-urea and then, with a second molecule of aniline, a diphenyl-urea and ammonia. The high temperature of the reaction is indeed sufficient to break the ring structure as here indicated:



From such decomposition in the presence of aniline we should naturally expect the results obtained by these investigators. Their attempts, however, to prepare similar compounds by the action of various nitriles upon urea met with no success.

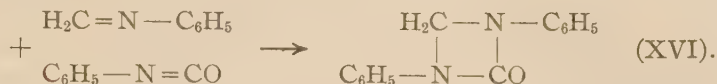
Of considerable interest in the cyclic-urea syntheses is the recent work of Senier and Shephard.¹⁷ The interaction of aryl thiocarbamides and aryl methylenediamines at 150–200° was found to produce quinazolines and also cyclic-ureas. When the para position in some one of the aryl groups is occupied by a substituent, quinazolines are formed, but when the para position is open or when isocyanates replace the thiocyanates,

²⁰ *Arch. der Pharm.*, **241**, 449 (1903).

²¹ *J. prakt. Chem.*, [2] **72**, 489 (1905).

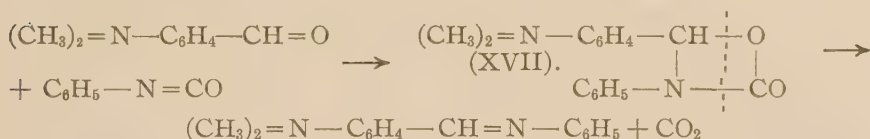
²² *Ibid.*, [2] **73**, 44 (1906).

cyclic methylene-ureas resulted. As the latter break up with ease their presence could be recognized only at such temperatures through a study of the decomposition products, namely—formaldehyde and the diaryl-ureas. In the case of methylenaniline and phenyl isocyanate, they found that the reaction proceeded at room temperature in a dry benzene solution, as indicated below:

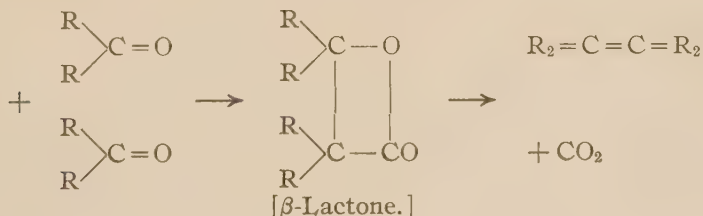


After a week or more a colorless product (XVI) separated out in crystalline form, melting at 198° . It was called methylene diphenylcarbamide. Though only sparingly soluble in the ordinary solvents, warming with acids or water affected hydrolysis into formaldehyde and symmetrical diphenyl-urea.

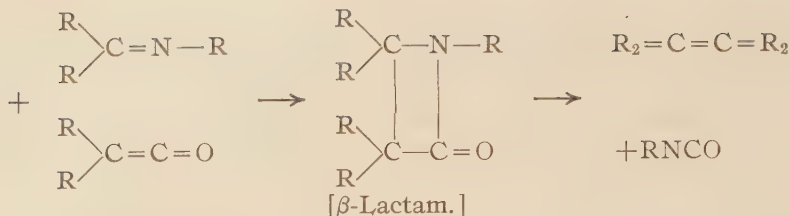
The action of phenyl isocyanate, as just discussed, at once recalls the property of ketenes to add to unsaturated compounds. This analogy has been brought out quite recently by Staudinger and Endle²³ and several examples were studied by way of illustration. With phenyl isocyanate and *p*-dimethylaminobenzaldehyde the reaction is shown below:



The condensation could not be accomplished at ordinary temperatures, but at 190° was easily effected. The condensation product, however, was at once subject to decomposition (as indicated by the dotted line) and the final result showed the presence only of *p*-dimethylaminobenzylidenaniline and carbon dioxide. These investigators consequently assumed that the four-membered heterocyclic ring (XVII) must have been produced as the intermediate step. This is evidenced by the close comparison between the reaction above and several of the regular ketene additions, as shown below:



²³ Ber., 50, 1042 (1917).



The decomposition of phenyl isocyanate addition product (XVII) is seen, therefore, to be strictly in conformity with the decomposition reactions as illustrated in each of the ketene addition products above cited. When these facts are considered, together with the results obtained by Frerichs and Hartwig (*loc. cit.*) there can be no longer any doubt concerning the product (XV) which these investigators obtained in the action of urea upon cyanoacetic ester.

The actual production of four-membered heterocyclic compounds containing two nitrogen and two carbon atoms alternately placed is no longer to be questioned. The doubt which heretofore has prevailed in the minds of chemists concerning the structure of the four-membered cyclic-ureas, as advanced by Schiff, has received its confirmation. There remains, therefore, the question, which must be solved for each compound under discussion, whether or not the characteristics of certain condensation products of ureas with aldehydes do or do not entitle these compounds to a position in the four-membered heterocyclic series. Numerous examples, where certain condensation products received their provisional constitutional formulas as derivatives of "methylene-urea," will gradually be found in which no real proof of structure is apparent save in analogy.

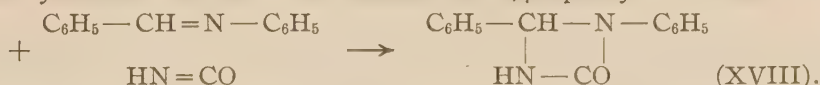
II. Theoretical Considerations.

While it has been known that aldehydes and ureas interact with the elimination of water, yet the nature of the reaction product has in most instances received little or no attention by the investigators. As previously stated, some have regarded the compounds produced as straight chain compounds of type (VI), while others have preferred to look upon them as cyclic compounds of type (V). Because of the physical properties of these aldehyde-urea condensation products, Bailey and Moore (*loc. cit.*) have suggested that they represent polymerized molecules possessing the general formula $(\text{CH}_2 = \text{N.CO.NH}_2)_x$. Working on the assumption that Schiff's ethylidene-urea is in reality the polymerized $\text{CH}_3.\text{CH} = \text{N.CO.NH}_2$, Bailey and Moore attempted to add hydrocyanic acid on to the molecule and also attempted its reduction with sodium amalgam in an alkaline alcoholic solution. The negative results obtained are explained by them as not due to a cyclic structure of the ethylidene-urea, which of course could not be expected to add a molecule of the acid or to

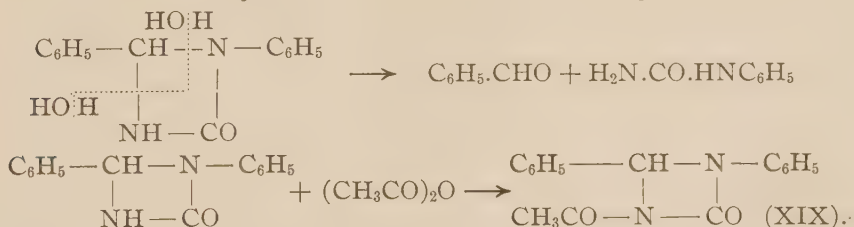
be reducible, but rather as due to the fact that depolymerization did not take place.

In our attempts to investigate the structure of a compound which we believe may belong to the four-membered cyclic-ureas but which, through the investigations of Bailey and Moore has been reported as a new and peculiarly constituted "triazolotriazole" (I) we were confronted on every hand with the greatest uncertainty concerning the structures of practically all compounds heretofore considered as four-membered cyclic-ureas. The one instance by Frerichs and Hartwig (*loc. cit.*) actually presents a type partially unsaturated, but in the work of Senior and Shephard (*loc. cit.*) we are given the only instances of isolation of two compounds of the saturated types. It fell to our lot, therefore, to investigate this subject from as many points of attack as possible and thus prepare a sure footing for subsequent work. We elected first the study of the addition of isocyanic acid to unsaturated compounds containing the $=C=N-$ complex or as we shall call it, the carbimino nucleus.

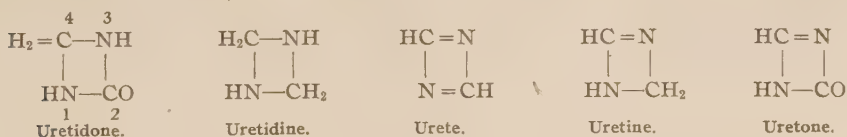
When benzylidenaniline is dissolved in glacial acetic acid and dry potassium cyanate is stirred into the ice-cold solution, one molecule of isocyanic acid slowly adds to the double linking and a crystalline precipitate separates after several hours. This product (XVIII) is a four-membered cyclic-urea and is to be considered as 1,4-diphenyl-uretidone.*



The compound was not obtained in quantitative yield, chiefly owing to the difficulty of securing its complete separation from the acid mixture. For this reason it is necessary to operate with as small a volume of acetic acid as possible. This diphenyl-uretidone is hydrolyzed by boiling with water (acids and alkalis also operate to this end) and the products are benzaldehyde and phenyl-urea exactly as required by the decomposition of a four-membered cyclic-urea of the structure already indicated.



* In this paper a new system of nomenclature suggested by Wm. J. Hale will be employed for four-membered heterocyclic compounds of this general type. The names and formulas are as follows:



This hydrolysis is also in agreement with the results of Senier and Shepherd (*loc. cit.*). We conclude, therefore, that the reaction between isocyanic acid and benzyldenaniline leads directly to a four-membered cyclic-urea of the atomic arrangement shown in Formula XVIII. In order to prove the presence of the one free imino hydrogen which Formula XVIII demands, we had only to boil the compound with acetic anhydride and fused sodium acetate when a beautifully crystalline monoacetyl derivative (XIX) was secured. This acetyl derivative, upon the new system of nomenclature, will be known as 3-acetyl-1,4-diphenyl-uretidone.

From the earlier publication by Dixon and Taylor (*loc. cit.*) we were led to believe that possibly phenyl-urea and benzaldehyde, the hydrolytic products of diphenyluretidone, might be made to condense directly to this original cyclo-urea. Equimolecular quantities of phenyl-urea and benzaldehyde when brought together in alcoholic solution condense to form a white, insoluble compound, immediately after the addition of a few drops of hydrochloric or sulfuric acid. The same result was obtained when equimolecular quantities of phenyl-urea and benzaldehyde were heated directly over a free flame. The white, insoluble condensation product gives, on analysis, results approximating very closely a benzyldene bisphenyl ureide,



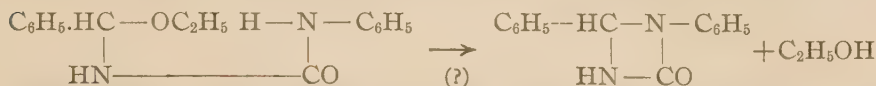
In the presence of dry hydrogen chloride, phenyl-urea and benzaldehyde in absolute alcoholic solution, condensed to a viscous red mass—a hydrochloride of a base containing an ethoxyl group. When this hydrochloride is diluted with alcohol and poured into cold water a flocculent, white precipitate is formed at once. This precipitate is a base which would appear to have the constitution



In their publication on thiourea Dixon and Taylor (*loc. cit.*) announced the formation of a base of similar structure. They considered the α -ethoxybenzyl group as directly attached to the sulfur atom of thiourea and regarded its transference to a nitrogen atom as a simple occurrence usually taking place upon long standing or gently heating the compound. In the product which we have prepared it would appear that the α -ethoxybenzyl group is attached to a nitrogen atom from the beginning or at least from the moment of precipitation of product as a free base. This is evidenced mainly from the comparative stability of the base upon long standing or upon gently heating, even up to its softening point ($150-5^\circ$). At this point a dissociation begins and a small amount of the benzyldene-bis-phenyl-ureide (previously mentioned) is produced. A partial transformation into this insoluble bis-phenyl-ureide takes place even when the base is boiled with absolute alcohol; benzaldehyde, of course, is liberated

at the same time in that only one molecule of benzaldehyde is required for condensation here with two molecules of the phenyl-urea simultaneously produced.

Dixon and Taylor describe the gradual transformation of their thiourea base into an insoluble "condensation product" as one of a ring closing and consequent formation of a cyclomethylene-thiourea. In the same manner we had hoped to secure a ring closing with our phenyl-urea base, by the loss of one molecule of alcohol, and thus obtain 1,4-diphenyl-uretidone.

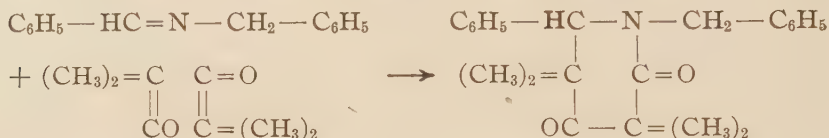


This change, however, could not be accomplished by the means at hand. There must be some condition whereby some of the ureas will condense with aldehydes to give four-membered cyclic-ureas. Certain it is that we have not been able to secure this ring structure when operating with phenyl-urea and benzaldehyde. It is doubtful also whether Dixon and Taylor actually had isolated a true four-membered cyclic-thiourea. The possibility still presents itself that their insoluble "condensation product" may have been formed through the loss of a molecule of alcohol from the carbon carrying the ethoxyl group and the adjoining nitrogen with a free hydrogen atom. A structure similar to that proposed by Dixon for "methylene-urea" is also within the possibilities. When our free ethoxyl base is dissolved in a very small quantity of glacial acetic acid there separates, after several hours, a semi-crystalline substance melting with decomposition at about 240°. This compound is very slightly soluble in alcohol or glacial acetic acid and is insoluble in other common solvents. Its properties might indicate that here was a compound similar to those obtained by Dixon and Taylor. As it has shown no properties distinctly characterizing it as a cyclic-urea we may assume that possibly this elimination of alcohol from the carbon-nitrogen linking, as suggested above for Dixon and Taylor's highly insoluble condensation products, may have occurred under these conditions. Tentatively we may assign to it the formula $\text{C}_6\text{H}_5.\text{NH}.\text{CO}.\text{N}:\text{CH}.\text{C}_6\text{H}_5$. Our analyses also would correspond with the requirements of this formula. Further work, however, will be required to place this formula outside the realms of speculation. From our present investigation, we are satisfied that the compound cannot come under the classification of cyclic-ureas or uretidones. The uretidones as a class are crystalline substances of no extensive range of insolubilities.

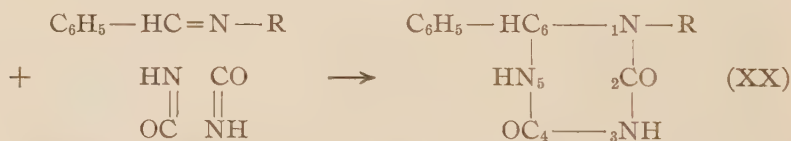
In the condensation of ketenes with an alkyl Schiff base, Staudinger²⁴ noted a different course of action from that with an aryl Schiff base. With the alkyl bases it was found that two molecules of a ketene con-

²⁴ *Ann.*, 374, 11 (1910).

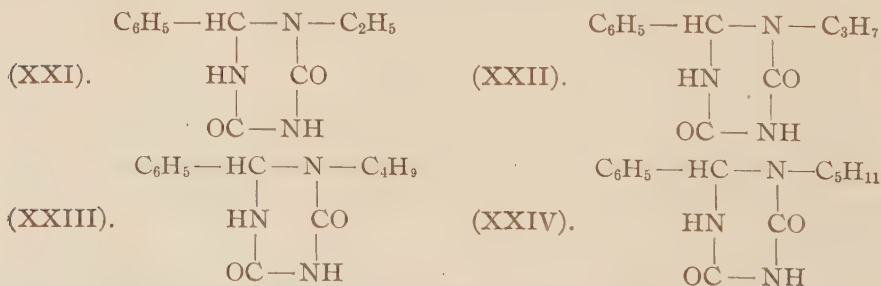
densed with one molecule of base and the principal product consisted of a derivative of piperidine. Thus with benzylidene-benzylamine and dimethyl ketene the reaction proceeded in a manner exactly analogous to the condensation of cyanic acid to cyanuric acid. The product was 1-benzyl-3,3,5,5-tetramethyl-6-phenyl-2,4-diketo-piperidine.



The similarity between ketenes and isocyanates at once suggested the possibility of a similar reaction between alkyl Schiff bases (with Schiff bases the nitrogen of the carbimino nucleus is attached directly to an alkyl or aryl group). For the study of this reaction we prepared the benzylidene derivatives of four normal primary alkyl amines by condensation of the latter with benzaldehyde. When these bases in glacial acetic acid solution are treated with potassium cyanate, we found no separation of product from the reaction mixture. The solution, however, after steam distillation and somewhat concentrated, gave a crystalline product which by analysis accorded with a derivative of cyanidine or symmetrical triazine (XX).



From benzylidene ethylamine, 1-ethyl-6-phenyl-2,4-diketohexahydrocyanidine (XXI); from benzylidene propylamine, the corresponding, 1-propyl derivative (XXII); from benzylidene butylamine, the corresponding, 1-butyl derivative (XXIII); and from benzylidene amylamine, the corresponding, 1-amyl derivative (XXIV) were obtained.



The properties of the cyanidine compounds above are in accord with the properties of a similar compound, a dimethyl-diketo-cyanidine, prepared

by Ostrogovich²⁵ and known heretofore under the name of acetoguanamide.

Our experiments, therefore, confirm the theoretical considerations of Staudinger and Endle (*loc. cit.*) regarding the addition of one molecule of isocyanic acid to one molecule of an aryl Schiff base, and further show that the compound as such can be isolated. They also carry the analogy between isocyanic acid and a ketene one step further and prove that with an alkyl Schiff base the addition of two molecules of a ketene to form a diketopiperidine is now strictly in accord with the addition of two molecules of isocyanic acid to a similar alkyl Schiff base to give in turn a diketocyanidine.

We have endeavored to condense isocyanic acid with compounds containing this carbimino nucleus where the nitrogen is attached to amino derivatives. For example, the compounds benzylidene phenylhydrazine, $(\text{C}_6\text{H}_5.\text{CH} : \text{N}.\text{NH}.\text{C}_6\text{H}_5)$, benzylidene as-diphenylhydrazine, $(\text{C}_6\text{H}_5.\text{CH} : \text{N}.\text{N} : (\text{C}_6\text{H}_5)_2)$, and also benzylidene benzylhydrazine,



were each investigated in this direction. Of these compounds neither the first nor the second showed any tendency to add cyanic acid at low temperatures and in glacial acetic acid solution. The first, however, is reported by Busch and Walter²⁶ as adding phenyl isocyanate to the imino position during warming to 170° after the manner of the Wöhler synthesis, producing 1-benzylidene-2,4-diphenylsemicarbazone. The imino hydrogen in the last named of the three semicarbazone compounds offers indeed a ready point of attack for isocyanic acid itself as has just recently been demonstrated by Bailey and Moore (*loc. cit.*) and the product resulting, or 1-benzylidene-2-benzylsemicarbazone,



no longer is able to add isocyanic acid. This general type of condensation of isocyanic acid with imino hydrogen has been investigated in detail by Busch and Walter (*loc. cit.*) and by Bailey and Read.²⁷ It would seem possible to effect the addition of isocyanic acid to a disubstituted (N)-amino derivative of the carbimino nucleus (*i. e.*, to the type $\text{R}_2\text{N} - \text{N} = \text{CHR}$) but more than likely phenyl isocyanate or other ethers of this acid will constitute the proper means of attack. Bailey and Moore already have reported the addition of isocyanic acid to benzalazine, a compound possessing two carbimino nuclei $(\text{C}_6\text{H}_5.\text{CH} = \text{N} - \text{N} = \text{CH}.\text{C}_6\text{H}_5)$. This will be discussed later.

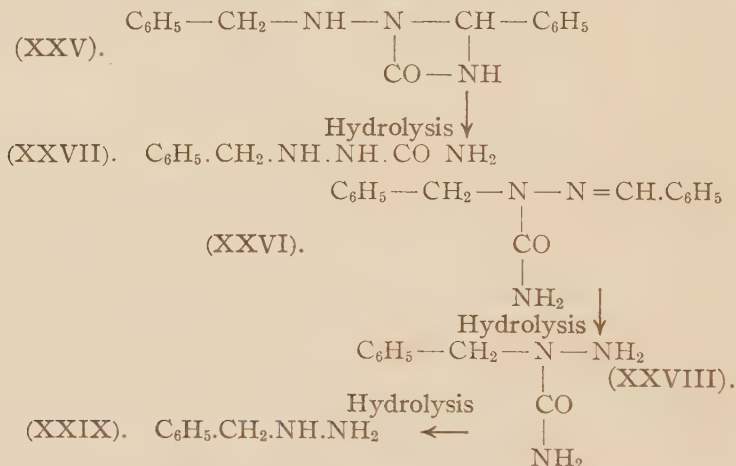
As previously stated, Bailey and Moore prepared 1-benzylidene-2-

²⁵ *Ann.*, **288**, 318 (1895).

²⁶ *Ber.*, **36**, 1360 (1903).

²⁷ *J. Am. Chem. Soc.*, **37**, 1884 (1915).

benzylsemicarbazone (XXVI) by the action of isocyanic acid upon benzylidene benzylhydrazone. Their description of the work, however, coupled with the statement that the product did not undergo hydrolysis when subjected to distillation with steam in the presence of a small amount of sulfuric acid raised considerable doubt in our minds as to the exact manner in which the isocyanic acid had attached itself. From what has been previously stated it may be inferred that isocyanic acid could add directly to the carbimino nucleus and result in a compound of structure (XXV). If, on the other hand, the attack took place on the imino hydrogen we should obtain the compound (XXVI) as reported by Bailey and Moore. In either case the product should be capable of hydrolysis with liberation of benzaldehyde and a semicarbazide,—1-benzylsemicarbazide (XXVII) if from a compound of formula (XXV) and 2-benzylsemicarbazide (XXVIII) if from a compound of formula (XXVI).



The semicarbazides XXVII and XXVIII have both been reported in the literature. The first (XXVII) was prepared by Kessler and Rupe²⁸ by the reduction of benzylidene semicarbazone



through the action of sodium amalgam and alcohol. The pure product melts at 155° and its hydrochloride at 178–180°. The second (XXVIII) was prepared by Curtius²⁹ through the action of isocyanic acid upon benzylhydrazine. The compound which Curtius obtained melted not sharply at 135°. He assigned to it the formula of a 1-benzylsemicarbazide (identical with XXVII). Its strong basic properties, however, led Busch, Opfermann and Walther³⁰ to identify it as a 2-benzylsemicarbazide

²⁸ *Ber.*, 45, 26 (1912).

²⁹ *J. prakt. Chem.*, [2] **62**, 97 (1900).

³⁰ *Ber.*, 37, 2325 (1904).

(XXVIII), which they reported as melting at 127–128°. Later the work of Kessler and Rupe (*loc. cit.*) eliminated all possibility of the Curtius formula for this compound in that they actually prepared the 1-benzylsemicarbazide (see above) whose properties in no wise tallied with those reported by Curtius. We must conclude, therefore, that isocyanic acid attacks preferably the imino hydrogen in benzylhydrazine (*i. e.*, at the α -nitrogen position). This has appeared to be a general conclusion for alkyl hydrazines but for aryl hydrazines the β -position (*i. e.*, the amino hydrogen) affords also a likely point of attack, the more stable type of compound thus resulting. If, as is common, the α -position is first attacked the more or less labile product may be transformed by gentle heat into the stable β -form. According to Busch, Opfermann and Walther (*loc. cit.*), if a benzoyl hydrazine is subjected to the action of mustard oil or an alkyl isocyanate, this strongly negative aroyl group forces the point of attack altogether upon the β -nitrogen position. The distinctly active character of the imino hydrogen as against the amino hydrogen may further be seen in the action of chloracetic acid upon hydrazinoacetic acid ($\text{H}_2\text{N}.\text{NH}.\text{CH}_2.\text{COOH}$) to give hydrazinodiacetic acid ($\text{H}_2\text{N}.\text{N}(:\text{CH}_2\text{COOH})_2$).³¹ Phenylhydrazine and chloracetic acid react similarly to give *as*-phenylhydrazinoacetic acid ($\text{H}_2\text{N}.\text{N}(\text{C}_6\text{H}_5).\text{CH}_2\text{COOH}$).

From the condensations just stated we may easily interpret the action of isocyanic acid upon benzylhydrazine as attacking the α -nitrogen position and leading to 2-benzylsemicarbazide as reported by Busch, *et al.* No statement, however, is made by these authors as to the possibility of transforming their 2-benzylsemicarbazide into a 1-benzylsemicarbazide. Their general rule indeed would seem to eliminate this possibility in that they state that methyl- or benzylhydrazine takes up mustard oil or alkyl isocyanates exclusively upon the α -nitrogen and the resulting 2,4-substituted compound (*e. g.*, $\text{C}_2\text{H}_5.\text{NH}.\text{CO}.\text{N}(\text{CH}_2.\text{C}_6\text{H}_5).\text{NH}_2$) does not suffer transformation into the 1,4-substituted compound (*e. g.*, $\text{C}_2\text{H}_5.\text{NH}.\text{CO}.\text{NH}.\text{NH}.\text{CH}_2.\text{C}_6\text{H}_5$). In such examples as phenyl isocyanate upon phenylhydrazine the 1,4-type of compound above results, as may be gathered from one of the preceding statements.³² In our experiments upon the 2-benzylsemicarbazide of Curtius and also Busch, *et al.*, we now find that a transformation of this semicarbazide into the 1,4-substituted form (*i. e.*, 1-benzylsemicarbazide) takes place simply upon melting of the former. In those cases where alkyl isocyanates were employed by Busch it may be assumed that the alkyl radical in the carbimino group affords greater stability to the molecule with the lack of any tendency to suffer this transformation. We prepared the 2-benzylsemi-

³¹ *J. prakt. Chem.*, [2] 83, 271 (1911); *J. Am. Chem. Soc.*, 36, 1747 (1914).

³² *Ber.*, 36, 1362 (1903).

carbazine by carefully adding potassium cyanate to a cold aqueous solution of benzylhydrazine hydrochloride. The crystalline product thus separating was dried *in vacuo* and found to melt between 126 and 135°. The slight solubility of 1-benzylsemicarbazide in cold chloroform and the ready solubility of the greater part of this product melting at 126–35° offered a simple means for the separation of the two semicarbazides. That part of this 126–35° product, which could be taken up in cold chloroform, was immediately precipitated therefrom, by the addition of ligroin, in small, flattened prisms melting at 135–36°. The minute portion remaining undissolved by the chloroform consisted chiefly of the higher melting semicarbazide, but its presence was sufficient to render difficult any attempts to determine the correct melting point. Curtius, however, possibly, by repeated and careful crystallizations, actually isolated the pure compound (m. p. 135°), whereas Busch, Opfermann and Walther undoubtedly had a compound slightly contaminated with a little of the 1-benzylsemicarbazide and hence the lower and inexact melting point, 127–8°.

When condensed with benzaldehyde at ordinary temperatures the pure 2-benzylsemicarbazide yielded the well known 1-benzylidene-2-benzylsemicarbazone (XXVI), melting at 155°, the same compound as reported by Busch, *et al.*, but with a slightly lower melting point (153–54°). When the 2-benzylsemicarbazide was melted and the cooled product crystallized from alcohol, beautiful glistening leaflets of 1-benzylsemicarbazide, melting at 155–56°, were obtained. This final product was now shown to be identical with the 1-benzylsemicarbazide prepared by Kessler and Rupe (*loc. cit.*); its hydrochloride, both when alone and when mixed with samples of the hydrochloride of the compound prepared by Kessler and Rupe, melted at the recorded point of 178–80°. There remains, therefore, no further question concerning the transformation of 2-benzylsemicarbazide into 1-benzylsemicarbazide at the point of fusion of the former. This transformation was, of course, accomplished in the case of the pure product (135°) as well as for the more or less impure mixture which one first obtains in the action of isocyanic acid upon benzylhydrazine (126–35°). Any chance that the two semicarbazides might have been formed simultaneously is thus eliminated.

With the matter thus cleared concerning the structure and isolation of 2-benzyl and 1-benzylsemicarbazide (XXVIII and XXVII), we saw at once the impossibility of proving anything concerning the structure of that addition product of isocyanate acid up benzylidene benzylhydrazine. Through the negative results obtained by us in our attempts to acetylate this addition product, we were forced to the conclusion that a cyclic-urea structure as a uretidone (shown in XXV) cannot likely be present. We have already remarked on the ease with which this latter

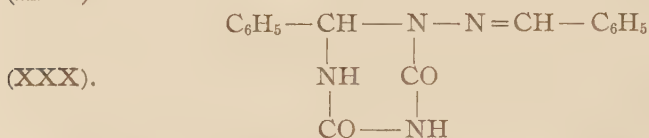
type of compound undergoes acetylation. Further than this, we may consider the hydrolysis which the compound suffers as not sufficiently speedy to indicate the presence of a uretidone.

The hydrolysis of the addition product (now to be considered as of structure XXVI) as carried out by Bailey and Moore was accomplished by a slight oxidation in the presence of sulfuric acid and neither benzaldehyde nor other products could be identified. We accomplished the hydrolysis by mixing the compound with dilute hydrochloric acid and subjecting this mixture to distillation with steam. The requisite quantity of benzaldehyde (1 mol.) is slowly liberated during long boiling, and the contents of the flask upon evaporation and recrystallization from alcohol, gave a compound melting at 110°. As it proved to be not the 2-benzylsemicarbazide (XXVIII) which we anticipated, we had only to look to the slight loss of carbon dioxide and ammonia during the distillation to anticipate yet another hydrolytic step with the final product easy of identification—that of benzylhydrazine (XXIX) in the form of its hydrochloride. A slight contamination of this hydrochloride with a dihydrochloride was noted; the latter is removed by its less degree of solubility in absolute alcohol. Pure benzylhydrazine hydrochloride is reported to melt at 111°. The pure product and that obtained by us from the hydrolysis when mixed melt at 110–111°. We identified our product conclusively by causing it to react with isocyanic acid in aqueous solution. The product, of course proved to be 2-benzylsemicarbazide (XXVIII), m. p. 135–36°.

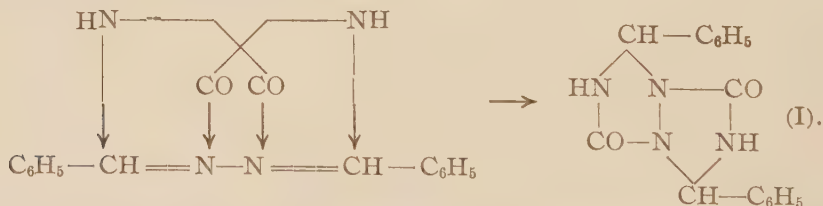
The addition of isocyanic acid to benzylidene benzylhydrazone is, therefore, to be interpreted in accordance with Formula XXVI, which Bailey and Moore have proposed. The hydrolysis of this 1-benzylidene-2-benzylsemicarbazone, however, is now seen to be possible and through its study we have come to a clear understanding concerning the stability of 1-benzylsemicarbazide over that of the corresponding 2-benzylsemicarbazide. The tendency of isocyanic acid to select an imino or amino hydrogen in hydrazine derivatives is more and more clearly shown to depend upon the nature of the substituents on the nitrogen atoms of the hydrazines; the more strongly negative substituents force the attack to the β -nitrogen position. In the case of individual amino derivatives a primary amine naturally takes preference over a secondary amine when open to action with isocyanic acid. In the carbimino nucleus again we note the great influence of a substituent either upon the nitrogen or upon the carbon atoms in directing the action of isocyanic acid. With an alkyl substituent upon the nitrogen atom only ketocyanidines result. When an aryl group is attached to the nitrogen atom only the uretidone is produced. None of these condensations, however, are likely to proceed when an amino group is attached to the nitrogen atom; no matter

whether the hydrogen atoms of the amino group are entirely replaced by aryl groups as seen above in the case of benzylidene as-diphenylhydrazine, or only one of the hydrogen atoms is so substituted as in benzylidene phenylhydrazine.

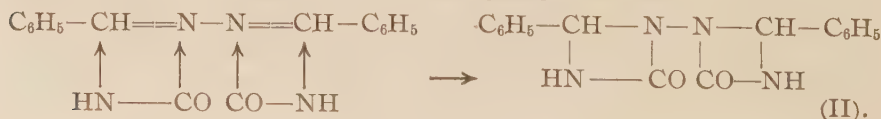
Bailey and Moore (*loc. cit.*) have shown that benzalazine, when dissolved in glacial acetic acid, readily takes up two molecules of isocyanic acid. They were at first inclined to look upon the addition compound so obtained as 1-benzylideneamino-6-phenyl-2,4-diketohexahydrocyanidine (XXX).



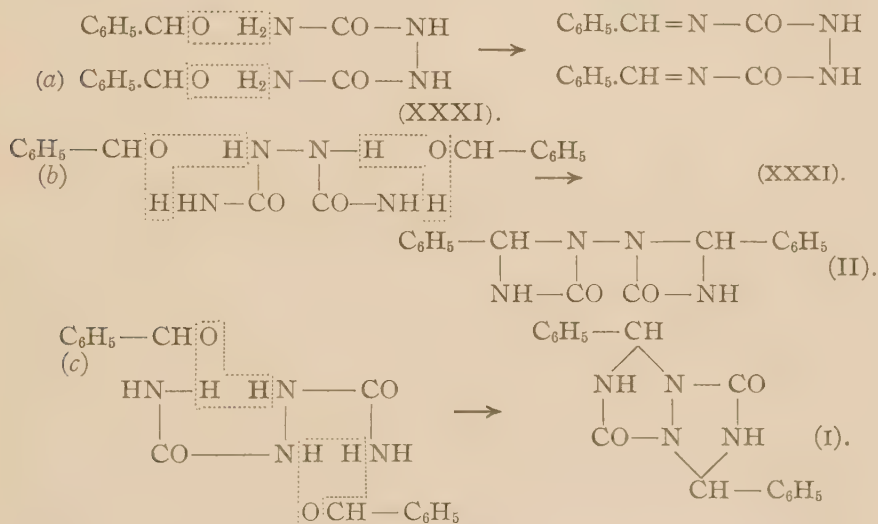
This condensation would be analogous to that previously described in the case of the alkyl Schiff bases. The compound, however, was found to be easily decomposed even by dilute acids and alkalis. This precludes all possibility of its being a triazine, for cyanuric acid and the previously mentioned cyanidine derivatives are exceedingly stable both towards acids and alkalis. Bailey and Moore's compound, upon heating with acetic anhydride and fused sodium acetate, readily forms a diacetyl derivative. We have found that compounds of the cyanidine type form only mono-acetyl derivatives under the same conditions; the hydrogen on the 3-nitrogen position being of an acid character due to the adjacent carbonyl groups remains unchanged. Moreover, one of the hydrolytic products was found to be hydrazodicarbonamide ($\text{NH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$), which showed that in the original compound a carbonyl group is attached to each nitrogen of the benzalazine rest. There are two other possible ways in which two molecules of isocyanic acid might add to benzalazine. The one is illustrated:



is what Bailey and Moore have termed a "crisscross addition" and shows the addition of isocyanic acid to form a five-membered ring; the other possible addition would produce a bis-diphenyl-uretidone:

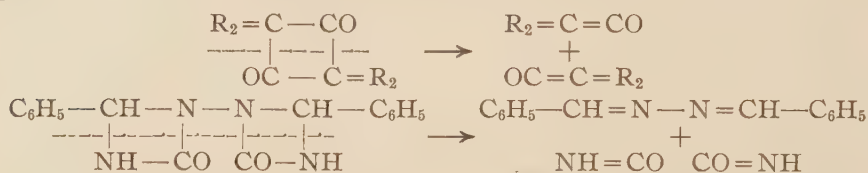


The work of Dixon and Taylor as well as Senier and Shepherd on four-membered ring production by the interaction of aldehydes and ureas, led us to attempt the preparation of the compound above by the condensation of benzaldehyde and hydrazodicarbonamide (the hydrolytic products of the benzalazine-cyanic acid addition compound). It was found possible to prepare the same compound by carrying out the reaction in alcoholic solution with dry hydrogen chloride. Similarly, the condensation of *p*-tolylaldehyde with hydrazodicarbonamide produced the same compound as obtained from the addition of isocyanic acid to *p*-tolylazine. However, the condensation of two molecules of benzaldehyde with one molecule of hydrazodicarbonamide may proceed in one of three ways (*a*, *b*, *c*):

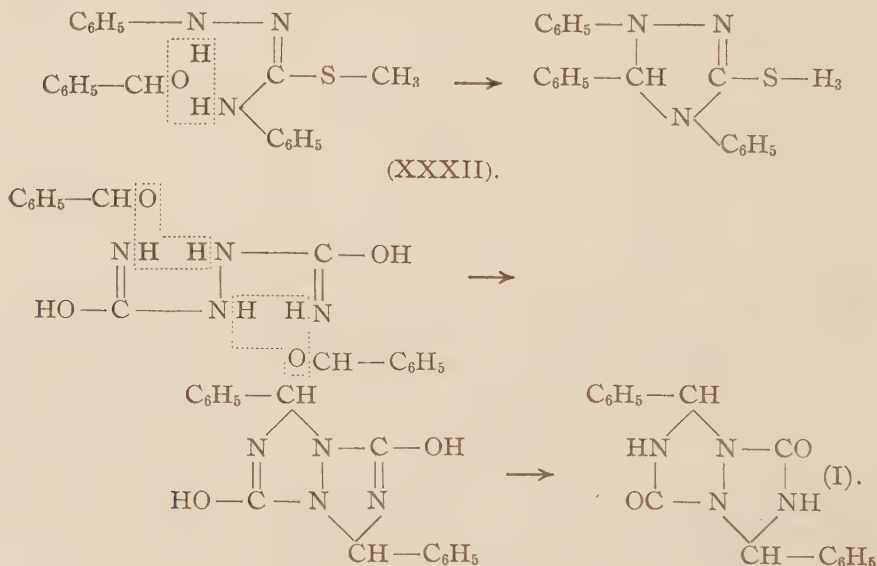


The formation of compound XXXI from benzalazine and isocyanic acid is very unlikely and this would tend to eliminate it as regards its formation from benzaldehyde and hydrazodicarbonamide. Compound II would be expected to be very susceptible to hydrolysis (and that most readily as reported by Bailey and Moore) as is seen in the behavior of the previously described 1,4-diphenyl-uretidone, which was prepared by an exactly analogous reaction from benzylidenaniline and isocyanic acid, but which we were unable to prepare by a condensation of its hydrolytic products (benzaldehyde and phenyl-urea). Compound II would also be very likely to yield a diacetyl derivative as reported. The melting point of the compound recalls the same general characteristics of four-membered cyclic compounds in decomposing gradually at about the point of fusion. The fact that the compound decomposes on melting into benzalazine and cyanic acid (two unsaturated products) seems to indicate structure II,

for this decomposition is analogous to the decomposition of four-membered rings obtained by the addition of ketenes to unsaturated compounds.³³ This may be illustrated as follows:



The formation of compound I from benzaldehyde and hydrazodicarbonamide recalls at once the formation of a five-membered ring by the condensation of benzaldehyde with the β -methyl ether of 1,4-diphenylsemicarbazide (XXXII) as reported by Busch and Holzmann.³⁴ The similarity between the two condensations is shown below:



The facts in favor of Formula I have been well summarized by Bailey and Moore and also by Bailey and McPherson,³⁵ but it would still seem that further work is necessary to establish beyond a doubt the true structure for their triazolotriazole.

III. Experimental Part.

Preparation of Potassium Cyanate.—The method employed was that of Bell,³⁶ in which absolute methyl alcohol is used for the extraction of

³³ Staudinger, "Die Ketene," 1912, p. 22; *Ber.*, **44**, 521 (1911).

³⁴ *Ber.*, **34**, 339 (1901).

³⁵ *J. Am. Chem. Soc.*, **39**, 1322 (1917).

³⁶ *Chem. News*, **32**, 99 (1875).

the mass left upon fusion of potassium dichromate and potassium ferrocyanide. In our work a Soxhlet extractor was used for removal of the potassium cyanate. Cotton plugs were placed in the outlet tube and in the top of the extraction thimble in order to hold back any of the finely divided ferric oxide from leaving the extraction chamber. The cyanate separating out of the alcohol solution was again extracted as before and thus a very pure product finally obtained.

Condensation of Isocyanic Acid and Benzylidenaniline. 1,4-Diphenyl-uretidone, $C_2H_2ON_2(C_6H_5)_2$ (XVIII).—Into a solution of 5 g. of benzylidenaniline in 20 cc. of glacial acetic acid, cooled by ice, an equal weight of finely pulverized potassium cyanate (over 2 mol.) was added in small portions at a time, and during constant stirring. The reaction mixture, which had become viscous during the operation, is then placed in a vacuum desiccator over soda-lime and the vessel set aside in an ice-box. If a white, amorphous product separates in a short time it should be removed by filtration and the mother liquor again set aside. This amorphous product often appears if the acetic acid is not kept ice-cold; it is due to a slight dissociation of the benzylidenaniline into its constituent parts with the consequent condensation of the aniline with isocyanic acid to give phenyl-urea and the subsequent condensation of this latter with benzaldehyde to yield the amorphous product—benzylidenebis-phenyl-ureide as described under another heading. After a day or more a crystalline product will have separated out of the cold concentrated acetic acid solution. In order to make this precipitation as nearly complete as possible it is well to use the smallest quantity of acetic acid. The product is purified by crystallization from 50% alcohol. 1,4-Diphenyl-uretidone is fairly soluble in alcohol, acetone or glacial acetic acid; slightly soluble in ethylacetate and insoluble in ether, chloroform, benzene, ligroin or water. The fine, colorless needles melt with decomposition at $224-5^\circ$.

Calc. for $C_{14}H_{12}ON_2$: C, 74.99; H, 5.39; N, 12.50. Found: C, 74.81; H, 5.54; N, 12.71.

1,4-Diphenyl-uretidone is without basic properties. Acids and alkalis as well as hot water slowly effect its hydrolysis into benzaldehyde and phenyl-urea. Thus when subjected to distillation with steam and the benzaldehyde thus removed the phenyl-urea in residuum in flask could be determined directly by applying the method of Liebig³⁷ for urea. The solution in the flask was cooled and titrated against a mercuric nitrate solution previously standardized against pure phenyl-urea using sodium carbonate as an external indicator. (1 cc. of the $Hg(NO_3)_2$ sol. here equivalent to 0.0116 g. phenyl-urea.)

Subst., 0.1605 g.; 8.5 cc. $Hg(NO_3)_2$ sol.

Calc. for $C_{14}H_{12}ON_2$: $1(NH_2.CO.NHC_6H_5)$, 60.73. Found: 61.44.

³⁷ Sutton, "Volumetric Analysis," 1900, p. 428.

The uretidone molecule is thus seen to include one molecule each of phenyl-urea and benzaldehyde. The presence of one replaceable hydrogen atom in the ring proper is proved by the formation of a monoacetyl derivative.

3-Acetyl-1,4-diphenyl-uretidone, $C_2HON_2(C_2H_5O)(C_6H_5)_2$ (XIX).—An equal weight of 1,4-diphenyl-uretidone and fused sodium acetate (about 1 g. each) together with a few cc. of acetic anhydride were heated for only a few minutes over a free flame. The solution was then poured upon ice when, during the slow decomposition of excess of acetic anhydride, the acetyl derivative separated out in excellent yield. The product, purified by crystallization from diluted acetic acid, melts at 237° . Acetyldiphenyl-uretidone is readily soluble in acetone, fairly soluble in alcohol, ethyl acetate or glacial acetic acid and insoluble in chloroform, benzene, ether, ligroin or water. It is much more stable than the free diphenyl-uretidone itself.

Calc. for $C_{16}H_{14}O_2N_2$: C, 72.14; H, 5.30; N, 10.53. Found: C, 72.01; H, 5.51; N, 10.71.

Condensation of Isocyanic Acid and Alkyl Schiff Bases.

The alkyl Schiff bases employed in this work were prepared by adding an equimolecular quantity of benzaldehyde to the alkyl amine in question (ethyl, *n*-propyl, *n*-butyl, *n*-amyl) at $5-10^\circ$ and drying the product over anhydrous potassium carbonate.

Benzylidene Ethylamine and Isocyanic Acid, 1-Ethyl-6-phenyl-2,4-diketohexahydrocyanidine, $C_3H_3O_2N_3(C_2H_5)(C_6H_5)$ (XXI).—To an ice-cooled solution of 2.5 g. of benzylidene ethylamine in 10 cc. of glacial acetic acid, is slowly added, during constant stirring, small quantities of potassium cyanate until a slight excess over two molecules have been used. The mixture is then set aside in a cool place for several days, after which it is transferred to a flask containing water and a few cubic centimeters of hydrochloric acid and subjected to distillation with steam. When no further trace of benzaldehyde is detectable in the distillate the solution in the flask is filtered, evaporated to a small volume and then allowed to cool; crystals of the cyanidine derivative are soon deposited. Recrystallization of this substance from alcohol gave a pure product melting at 226° . This ethyl-phenyldiketocyanidine is readily soluble in glacial acetic acid; fairly soluble in alcohol, acetone, chloroform, ethyl acetate or water, crystallizing from each; it is slightly soluble in ether or benzene and insoluble in ligroin.

Calc. for $C_{11}H_{13}O_2N_3$: C, 60.27; H, 5.98; N, 19.18.

Found: C, 60.21; H, 6.19; N, 19.27.

This diketo-sym-triazine gives a flocculent precipitate with silver nitrate. As previously stated, this substance corresponds closely in its properties to the compound prepared by Ostrogovich,—a compound pre-

pared by condensing urea with acetylurethane. The compounds are closely similar but in the one only a tetrahydro ring is present, whereas in the compound above we describe the completely reduced or hexahydro ring.

Benzylidene Propylamine and Isocyanic Acid, 1-Propyl-6-phenyl-2,4-diketo-hexahydrocyanidine, $C_3H_7.C_3H_3O_2N_3.C_6H_5$ (XXII).—Benzylidene-*n*-propylamine was digested with potassium cyanate in a cold glacial acetic acid solution in exactly analogous manner to that described above for the preparation of ethyl-phenyldiketocyanidine. The final crystalline product crystallized from alcohol melts at 211° . This compound is readily soluble in acetic acid; fairly soluble in alcohol, chloroform, acetone, ethyl acetate; slightly soluble in ether, benzene or water; and insoluble in ligroin.

Calc. for $C_{12}H_{15}O_2N_3$: C, 61.77; H, 6.48; N, 18.03.

Found: C, 61.76; H, 6.58; N, 18.38.

1-Propyl-6-phenyl-5-acetyl-2,4-diketo-hexahydrocyanidine, $C_3H_7.C_3H_2O_2N_3(COCH_3).C_6H_5$.—When the propyl-phenyldiketocyanidine obtained above is boiled for a few minutes with acetic anhydride and fused sodium acetate and the mixture poured upon ice, a crystalline mon-acetyl derivative is readily obtained. The compound may be purified by crystallization from 80% alcohol. The small, colorless crystals melt at 120° . It is readily soluble in almost all of the organic solvents; only fairly soluble in ligroin and insoluble in water. The determination of carbon and hydrogen could not lead to definite conclusions. A nitrogen determination, however, sufficed to show the presence of only one acetyl group, more than likely in the 5-position. The hydrogen in the 3-position with a carbonyl group at either side would react decidedly acid and its replacement by acetyl would no doubt require the formation first of a silver salt and subsequent treatment with acetyl chloride—the general method of procedure in acetylation of cyanidines.

Calc. for $C_{14}H_{17}O_3N_3$: N, 15.27.

Found: N, 15.43.

Benzylidene Butylamine and Isocyanic Acid, 1-Butyl-6-phenyl-2,4-diketo-hexahydrocyanidine, $C_4H_9.C_3H_3O_2N_3.C_6H_5$ (XXIII).—Benzylidene-*n*-butylamine was digested with potassium cyanate in cold glacial acetic acid in exactly analogous manner to that described above for the preparation of the ethyl and propyl derivatives. The final crystalline product crystallized from alcohol melts at 188° . It is readily soluble in acetic acid; fairly soluble in alcohol, chloroform, acetone, ethyl acetate; slightly soluble in ether, benzene or water, and insoluble in ligroin.

Calc. for $C_{13}H_{17}O_2N_3$: C, 63.13; H, 6.93; N, 17.00.

Found: C, 63.41; H, 7.03; N, 17.10.

Benzylidene Amylamine and Isocyanic Acid, 1-Amyl-6-phenyl-2,4-diketo-hexahydrocyanidine, $C_5H_{11}.C_3H_3O_2N_3.C_6H_5$ (XXIV).—Benzylidene-

dene-*n*-amylamine was here digested with potassium cyanate in cold glacial acetic acid solution and the operation carried out exactly as described for the preceding ketocyanidines. It was purified by crystallization from alcohol and melts at 202°. It is readily soluble in acetic acid, chloroform or acetone; fairly soluble in alcohol, ethyl acetate; slightly soluble in ether, benzene or water; and insoluble in ligroin.

Calc. for $C_{14}H_{19}O_2N_3$: C, 64.34; H, 7.33; N, 16.09.

Found: C, 64.49; H, 7.43; N, 16.37.

Condensation of *p*-Tolylazine and Isocyanic Acid.—To 10 g. of *p*-tolylazine in 50 cc. of glacial acetic acid are added in small portions about 10 g. of potassium cyanate. The solution which is cooled by an ice bath is well stirred during the addition of the cyanate. The solution gradually becomes viscous due to the separation of the addition compound. After several hours the reaction mixture is filtered and the precipitated addition compound washed several times with water. For purification the product is recrystallized from alcohol. Its solubilities are very close to those of the benzalazine-cyanic acid addition compound reported by Bailey and Moore (*loc. cit.*). It melts with decomposition at 212–214° (uncorr.) and forms a diacetyl derivative when boiled with acetic anhydride and fused sodium acetate which melts at 150° (uncorr.).

Calc. for $(CH_3.C_6H_4.CH:N)_2.2HNCO$: C, 67.05; H, 5.63; N, 17.39.

Found: C, 67.60; H, 5.98; N, 17.06.

Analysis of the diacetyl derivative gave the following results:

Calc. for $C_{22}H_{22}O_4N_4$: C, 65.00; H, 5.46; N, 13.79.

Found: C, 65.03; H, 5.35; N, 14.01.

Hydrolysis of 1-Benzylidene-2-Benzylsemicarbazone, $C_6H_5.CH_2.N(CO-NH_2).N$: $CH.C_6H_5$.—This compound was prepared according to the directions of Bailey and Moore (*loc. cit.*), by first reducing benzalazine with sodium amalgam and then treating the reduced product (benzylidene benzylhydrazone) with potassium cyanate in cold glacial acetic acid solution. The substance thus separating out may be crystallized from ether and melts at 155.5°, or practically 156°, as reported by Bailey and Moore. It is readily soluble in most organic solvents, but only slightly soluble in ligroin. When placed in a flask containing a little water and hydrochloric acid and subjected to distillation with steam, the product is slowly hydrolyzed. This process was continued until the distillate no longer contained benzaldehyde, after which the contents of the flask were filtered and finally evaporated to dryness upon a water bath. The dry residue was next boiled with a small amount of absolute alcohol and the clear filtrate from the insoluble portion (the dihydrochloride of benzylhydrazine), allowed to cool. The crystals of benzylhydrazine hydrochloride appeared in glistening leaflets melting at 110°. Pure benzylhydrazine hydrochloride melts at 111°; a mixture of the latter and the sample we obtained from the

hydrolysis melted at 110–11°. In all respects the hydrolytic product checked with the properties of pure benzylhydrazine hydrochloride. The hydrolysis, therefore, may be interpreted as proceeding in the manner previously indicated—(XXVI), (XXVIII), (XXIX).

When the final hydrolytic product (*i. e.*, the benzylhydrazine hydrochloride) was dissolved in a very small amount of water and a little more than an equimolecular quantity of potassium cyanate added to the solution there precipitated after a short time colorless crystals melting at 130–135°, in agreement with the results found by Busch, *et al.* (*loc. cit.*) when isocyanic acid was condensed with benzylhydrazine to give 2-benzylsemicarbazide (m. p. 135–36°). A sample prepared according to the method of Busch melted at 130–35° and when mixed with our product above the mixture likewise melted at 130–35°. There would seem to be no doubt concerning the identity of the two compounds—that prepared according to Busch and that obtained by the action of isocyanic acid upon the hydrolytic product.

Calc. for $C_8H_{11}ON_3$: C, 58.15; H, 6.71; N, 25.45.

Found: C, 58.39; H, 6.87; N, 25.23.

Preparation of Pure 2-Benzylsemicarbazide, $C_6H_5.CH_2.N(NH_2).CO.NH_2$ (XXVIII).—The action of potassium cyanate upon an aqueous solution of benzylhydrazine hydrochloride is reported by Curtius (*loc. cit.*) to give 1-benzylsemicarbazide, melting at 135°. The product of this same reaction as carried out by Busch, Opfermann and Walther (*loc. cit.*) is construed as a 2-benzylsemicarbazide melting at 127–128°. Kessler and Rupe (*loc. cit.*) prepared the pure 1-benzylsemicarbazide (m. p. 155°) as described in our theoretical considerations. When potassium cyanate is added to an ice-cold concentrated aqueous solution of benzylhydrazine hydrochloride (in equimolecular quantities), the crystals of 2-benzylsemicarbazide are at once precipitated. Filtered off and dried *in vacuo*, the product melts at 126–135°. These crystals were now mixed with ice-cold chloroform and the mixture filtered immediately by suction, pouring a little chloroform also upon the filter to insure removal of the last traces of soluble material. Upon the addition of ligroin to this chloroform filtrate small, glistening, colorless, flat prisms of 2-benzylsemicarbazide appear. The product may be again taken up in chloroform and precipitated by ligroin but the melting point is not changed—135–36°. 2-Benzylsemicarbazide is readily soluble in alcohol, acetone, chloroform, ethylacetate or glacial acetic acid; fairly soluble in benzene or water; slightly soluble in ether and insoluble in ligroin. This semicarbazide does not reduce Fehling's solution in the cold, even after several days' standing, but upon warming the reduction is accomplished slowly. At the temperature of its melting point it is transformed into 1-benzylsemicarbazide.

Preparation of 1-Benzylsemicarbazide, $C_6H_5.CH_2.NH.NH.CO.NH_2$ (XXVII).—When 2-benzylsemicarbazide is heated in an air bath to the point of fusion for a few minutes and the cooled product then crystallized from a 20% alcohol, colorless prisms of 1-benzylsemicarbazide are obtained. These crystals are not so flattened nor so small as those of 2-benzylsemicarbazide. Both the melting point (155°) and the physical properties of this product are identical with the compound prepared by Kessler and Rupe. 1-Benzylsemicarbazide is readily soluble in alcohol, acetone or glacial acetic acid; fairly soluble in chloroform, ethyl acetate or water; slightly soluble in benzene or ether and insoluble in ligroin. These solubilities differ somewhat from those of the 2-benzylsemicarbazide. In cold chloroform very little of the product dissolves and hence a means of separating the two semicarbazides is afforded. This semicarbazide begins to reduce Fehling's solution even in the cold and reduces it readily upon warming, as recorded by Busch, *et al.* A sample of this semicarbazide and an equal quantity of 2-benzylsemicarbazide when mixed melted as low as $120-24^\circ$, thus affording an explanation of the indefinite results obtained by other investigators.

Action of Isocyanic Acid upon *N*-Amino Derivatives of the Carbimino Nucleus.—As previously stated, the compounds here subjected to the action of isocyanic acid failed to condense with the latter at low temperatures and in glacial acetic or propionic acids. Benzylidene as-diphenylhydrazine ($C_6H_5.CH : N.N : (C_6H_5)_2$) was brought into reaction under these conditions and also in a mixture of benzene and acetic acid in order to increase its solubility in the reduction medium. No reaction could be detected. In a similar manner, benzylidene phenylhydrazone ($C_6H_5.-CH : N.NH.C_6H_5$) was found to be unreactive toward isocyanic acid, but as discussed in our theoretical considerations, this compound does condense with phenyl isocyanate at high temperatures. 1-Benzylidene-2-benzylsemicarbazone as also previously discussed, failed to condense further with isocyanic acid. Though the carbimino nucleus is a favored complex for condensation with isocyanic acid it is to be noted that certain substituents on the nitrogen atom may considerably retard this tendency for condensation.

Condensation of Benzaldehyde and Phenyl-urea. Benzylidene-bis-phenyl-ureide, $C_6H_5.CH : (NH.CO.NHC_6H_5)_2$.—Phenyl-urea and benzaldehyde were brought into solution by gentle warming over a free flame. Condensation took place immediately with the production of a white, gelatinous mass. Variation in the quantity of either component in the original mixture did not appear to produce any appreciable change in the composition of the final product. The compound was thoroughly washed with cold water, then with alcohol and finally with ether and dried *in vacuo*. It melted with decomposition at $198-9^\circ$. This benzyli-

dene-bis-phenylureide is only slightly soluble in alcohol, acetone or ethylacetate and practically insoluble in chloroform, ether, benzene, ligroin or water. It is fairly soluble in glacial acetic acid but with dissociation.

Calc. for $C_{21}H_{20}O_2N_4$: C, 69.97; H, 5.60; N, 15.56. Found: C, 69.40; H, 5.88; N, 15.23.

This same product may also be prepared by dissolving phenyl-urea and benzaldehyde in a small quantity of alcohol and adding a few drops of conc. sulfuric acid which effects immediate condensation. The final product is identical with that prepared above.

Calc. for $C_{21}H_{20}O_2N_4$: N, 15.56. Found: N, 15.71.

Water itself does not work disadvantageously toward this condensation as evidenced in the production of this same bisphenylureide when phenyl-urea and benzaldehyde are mixed with water and a few drops of conc. hydrochloric acid added. The final product is again identical with those just described.

Calc. for $C_{21}H_{20}O_2N_4$: N, 15.56. Found: N, 15.41.

Benzylidene-bis-phenylureide is hydrolyzed by warm water; acids or alkalies accomplish this result more readily. In order to determine the relative amount of phenyl-urea to benzaldehyde entering into the condensation, resort was again made to distillation with steam and titration of residuum in flask against the mercuric nitrate solution previously standardized against pure phenyl-urea (1 cc. standard sol. = 0.0116 g. phenyl-urea). Samples of the product prepared by either of the three methods gave identical values according with the constitution of a diphenylureide. The analysis reported below was made with a sample prepared without the use of a solvent.

Subst., 0.2348 g.; 15.5 cc. $Hg(NO_3)_2$ sol.

Calc. for $C_{21}H_{20}O_2N_4$: $2(NH_2.CO.NHC_6H_5)$, 75.57. Found: 76.60.

Condensation of Benzaldehyde and Phenyl-urea in the Presence of Absolute Alcohol and Hydrogen Chloride.

(a) α -Ethoxybenzyl-phenyl-urea Hydrochloride, $(C_6H_5NH.CO.NH.CH(OC_2H_5)C_6H_5)HCl$.—Two g. of phenyl-urea (1 mol.) and 2 g. of benzaldehyde (1.3 mol.) were mixed with 6–7 cc. of absolute alcohol and the mixture, thoroughly cooled, then saturated with dry hydrogen chloride. The final yellow solution was placed in a vacuum desiccator over sulfuric acid for one day and on the following day in a similar desiccator over soda-lime. The next day it was again transferred to the acid-filled desiccator and this alternation continued for a week, or more, when the mass became viscous and gave no odor of hydrogen chloride or benzaldehyde. A portion of this product was then dissolved in 95% alcohol and slightly diluted with freshly distilled water. The mixture (containing the free base as a

precipitate) was at once titrated against $N/10$ alkali (using phenolphthalein as indicator). The result indicates distinctly a monohydrochloride of the free base.

Subst., 1.461 g.; cc. $N/10$ NaOH, 46.2.

Calc. for $C_{16}H_{18}O_2N_2 \cdot HCl$: 1(HCl), 11.90. Found: HCl, 11.53.

(b) α -Ethoxybenzyl-phenyl-urea, $C_6H_5NH \cdot CO \cdot NH \cdot CH(OC_2H_5)C_6H_5$.—A portion of the hydrochloride of the condensation product, as just described, was dissolved in an equal volume of alcohol and then slowly poured into cold water. The precipitated free base, dried on a porous plate, was again taken up in alcohol and again precipitated by pouring the solution into water. This non-crystalline substance, thus purified, softens upon heating to $150-5^\circ$. The compound is readily soluble in glacial acetic acid, alcohol, or acetone; it is very slightly soluble in ethyl acetate or chloroform and practically insoluble in ether, benzene, ligroin or water.

Calc. for $C_{16}H_{18}O_2N_2$: C, 71.06; H, 6.71; N, 10.37. Found: C, 71.81; H, 6.59; N, 10.97.

When subjected to distillation with steam, hydrolysis was easily effected and the phenyl-urea left in flask was titrated against the same mercuric nitrate solution previously standardized against pure phenyl-urea (1 cc. sol. = 0.0116 g. phenyl-urea).

Subst., 0.1252; 5.5 cc. $Hg(NO_3)_2$ sol.

Calc. for $C_{16}H_{18}O_2N_2$: 1($NH_2 \cdot CO \cdot NHC_6H_5$), 50.35. Found: 50.95.

The free base is comparatively stable under ordinary conditions. Warming its absolute alcoholic solution always gave a small amount of flocculent precipitate which proved to be benzylidene-bis-phenylureide. Upon heating the compound to the point where softening just begins and then taking up the mass in absolute alcohol a considerable amount of benzylidene-bis-phenylureide remained undissolved. This free base did not show any great tendency to go over into an insoluble product which might be compared with the insoluble products described by Dixon and Taylor (*loc. cit.*) as resulting from their ethoxyl thiourea bases. The only condition by which our free base was transformed into a semi-crystalline high melting ($235-240^\circ$) substance was found to arise when its conc. solution in glacial acetic acid was allowed to stand several hours. There separated from this medium a substance very slightly soluble in alcohol or acetic acid and practically insoluble in the other organic solvents. Though the product analyzed for a compound of the same empirical formula as 1,4-diphenyluretidone, it did not possess any of the properties of this true cyclic-urea which nevertheless we had hoped to prepare from this free base. Our ring closing therefore had not proceeded in the manner outlined by Dixon and Taylor (*loc. cit.*) and the insoluble product was not further investigated.

Calc. for $C_{14}H_{12}ON_2$: C, 74.99; H, 5.39; N, 12.50. Found: C, 74.41; H, 5.53; N, 12.60.

Condensation of Hydrazodicarbonamide and Benzaldehyde. Preparation of Bis-benzylidene-urea or the Bailey and Moore Twin Triazole.—0.3 g. of hydrazodicarbonamide and 0.4 g. of freshly distilled benzaldehyde were dissolved in 20 cc. of absolute alcohol. This solution, which was well cooled with an ice-salt mixture, was then saturated with dry hydrogen chloride. After this solution had stood for an hour at room temperature it was again saturated with hydrogen chloride, but this time no attempt was made to cool the solution while the gas was passed through. It was then filtered and the filtrate allowed to evaporate spontaneously until considerable solid material had separated and there was very little solvent. After filtering with suction, the precipitate was washed with cold water to remove the hydrogen chloride. The greater part of the benzaldehyde and benzoic acid was removed by several washings with ether. The precipitate was then thoroughly digested with a dilute solution of sodium carbonate and then recrystallized from alcohol. The substance prepared in this way had a melting point of 229° and the following solubilities: Slightly soluble in ether or chloroform; fairly soluble in ethyl acetate, acetone, alcohol, or glacial acetic acid; insoluble in ligroin or water. The solubilities were found to be identical with those of the benzalazine-cyanic addition product prepared by Bailey and Moore (*loc. cit.*). They report a melting point of 234° , although we found that the substance prepared by their method from benzalazine and isocyanic acid has a melting point of 231° . A mixture of equal parts of the substances prepared by the two different methods has a melting point of 230° .

Calc. for $C_{16}H_{14}N_4O_2$: C, 65.31; H, 4.76; N, 19.05.

Found: C, 65.40; H, 4.84; N, 19.19.

There is no doubt that the condensation of benzaldehyde and hydrazodicarbonamide produces the same compound which Bailey and Moore obtained from the addition of isocyanic acid to benzalazine. This is further confirmed by the formation of the same diacetyl derivative and the same oxidation product from the compound prepared by either of the two methods.

Diacetyl Derivative of the Hydrazodicarbonamide and Benzaldehyde Condensation Product.—A solution of the condensation product in acetic anhydride is boiled for an hour with a small amount of fused sodium acetate. After cooling it is diluted to three times its volume with water. The excess of acetic anhydride was removed by warming the solution. On cooling, the acetyl derivative separates in excellent yield. Its solubilities were found to be identical with those of the diacetyl derivative of the benzalazine-cyanic acid addition compound. For analysis the substance was precipitated from its benzene solution with ligroin and recrystallized from alcohol. The crystals so obtained soften about 140° and melt with decomposition at 167° .

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